Harnessing the reactivity of alkenyl heteroarenes through copper catalysis and Lewis acids

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Chapter 3

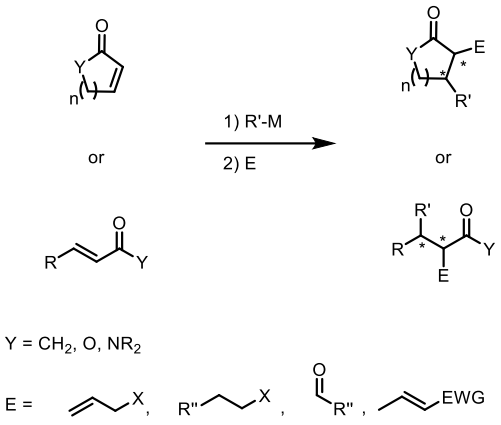
Hetero Aromatic Enolate Trapping Promoted by $BF_3.OEt_2$

In this chapter, the development of a one-pot Michael/Michael addition tandem reaction is discussed. The process exhibits remarkable chemoselectivity and unexpected inversion of the reactivity order. Wide range of alkenyl heterocycles, as substrates, and enoates, as trapping agents, have been tested in the protocol. Furthermore, selected NMR studies have been conducted to clarify the origin of the high selectivity found in the process.

Manuscript in preparation

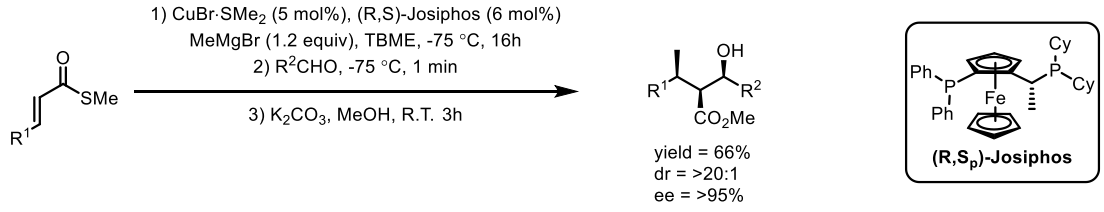
3.1 Introduction

Electrophilic trapping of enolate deriving from the addition of various electrophiles to Michael acceptors is a well-known methodology in synthetic chemistry.[1] This approach not only allows to access complex structures in a direct way avoiding extra purification steps, but it is also a straightforward way for the construction of contiguous stereocentres. Among all the possible nucleophiles that can be employed in these transformations, organometallic reagents are one of the most common, yielding highly reactive metal-enolates.[2] Typical substrates for this transformation are α,β-unsaturated carbonyl compounds, such as ketones,[3] esters,[4] thioesters[5] and cyclic lactams,[6] while commonly used electrophiles are alkylating agents, such us alkyl and allyl halide, or aldehydes leading to 1,4/aldol addition tandem process (Scheme 1).



Scheme 1: Conjugated addition to carbonyl compounds followed by enolate trapping.

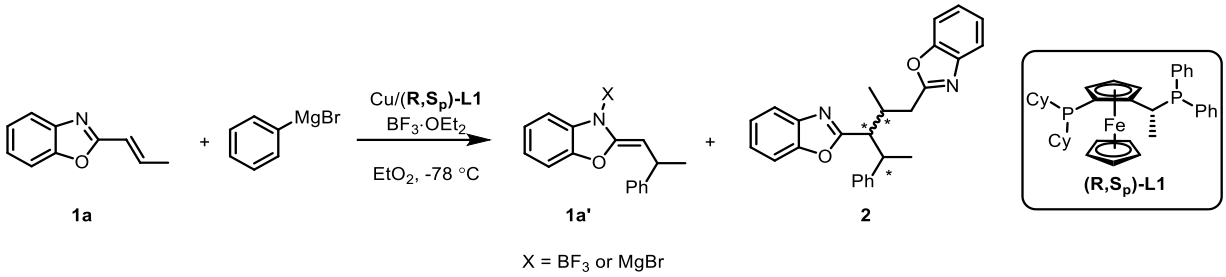
The control over the absolute and relative stereochemistry of the final product as well as over the reactivity of the enolate represents the major challenge in this type of transformation. Common strategies to overcome this problem are 1) the design of specific substrates bearing both the Michael acceptor and the electrophilic moiety in their structures (intramolecular trapping),[7] 2) the use of more rigid structure such as cyclic substrates (intermolecular trapping).[2,3,4] One of the first example of highly stereoselective 1,4/aldol addition tandem process using acyclic Michael acceptors and organometallic reagent, has been reported by Feringa and co-workers in 2006 (Scheme2).[5]



Scheme 2: Copper catalysed conjugate addition to acyclic thioesters and aldol trapping.

Despite the continuous progress in the field of asymmetric catalysis, trapping of metal-enolate still presents a challenge that needs to be addressed. To improve the outcome of the process in terms of selectivity and reactivity, often use of co-solvents and external additives, such as hexamethylphosphoramide (HMPA) or 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinon (DMPU) is required. Furthermore, use of acyclic substrates is still an unsolved issue and only few reports had appeared in the literature since the 2006.[2c] During our study on copper catalysed conjugate addition of Grignard reagents to alkenyl aromatic heterocycles,[8] in some specific reactions we encountered the formation of unknown side product in significant amount.

Isolation and full characterization of the latter led us to identify it as compound **2**, resulting from the trapping of enolate **1a'** with another molecule of substrate **1a** (Scheme 3). Hereinafter in this chapter, the process leading to the formation of compound **2** will be referred as "auto-trapping".

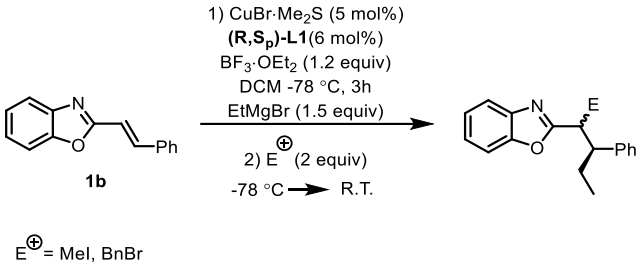


Scheme 3: Auto-trapping of **1a** upon conjugate addition of PhMgBr.

Despite the presence of three stereocentres, and thus the possibility to form eight different stereoisomers, remarkably compound **2** was formed as a single diastereoisomer with high enantioselectivity (*ee* = 97%). This unexpected reactivity made us wondering, if it is possible to use different electrophiles in this transformation. In the next sections, the reactivity of different alkenyl heterocycles towards sequential asymmetric conjugate additions (ACA)/ enolate trapping process in combination with several electrophiles will be discussed.

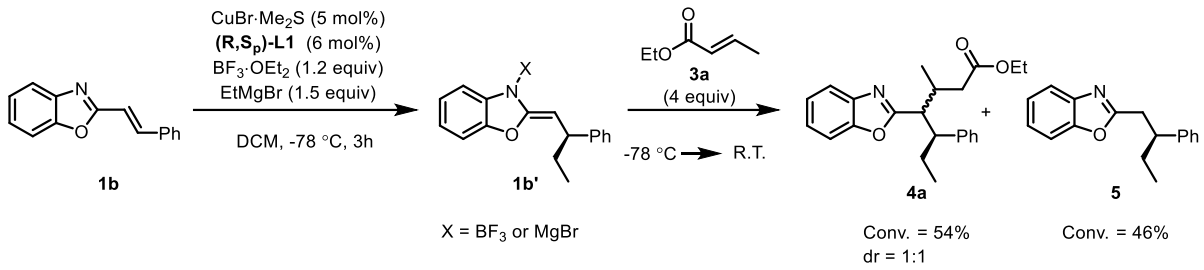
3.2 Results and Discussion

We started our investigation testing commonly used highly reactive electrophiles, such as methyl iodide and benzyl bromide for sequential trapping of enolate generated from benzoxazole derivative **1b** (Scheme 4).



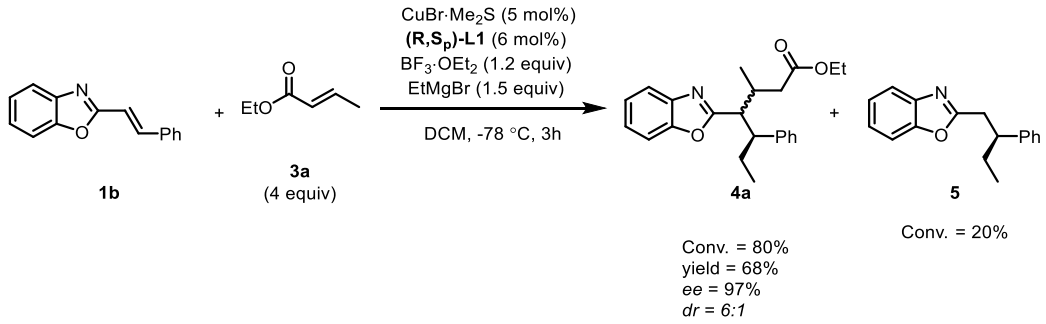
Scheme 4: Sequential ACA/enolate trapping of **1b** with alkylating agents.

Surprisingly, none of the reactions furnished the desired trapping product, but only the 1,4 adduct was obtained. On the other hand, the use of benzaldehyde as electrophile gave 30% conversion towards the desired enolate trapping product. Being the stereocentre at β-position formed with high enantioselectivity (96%), in the above process only 4 diastereoisomers can be theoretically formed. Remarkably, in the NMR crude only 2 of them were detected in 2:1 ratio. Despite the high reactivity of the electrophiles employed, the results were not comparable with the "auto-trapping" process encountered before. This led us to consider the use of a Michael acceptor as trapping agent. When ethyl crotonate **3a** was used as trapping agent in the same reaction conditions, we were pleased to detect 54% conversion towards product **4a**. Also in this case only two diastereoisomers where detected in 1:1 ratio (Scheme 5).



Scheme 5: Sequential ACA/enolate trapping of **1b** with ethyl crotonate **3a**.

The higher conversion indicate that the enolate **1b'** has greater affinity with soft nucleophiles such as electron deficient olefins in Michael acceptors than with alkyl halides. In order to improve the diastereoselectivity, the second step was performed at keepimg the temperature steadly at -78 °C. The low temperature was indeed beneficial and the *dr* increased from 1:1 to 6:1 without affecting the conversion. Driven by intuition and in order to reproduce as much as possible the reaction conditions in which the "auto-trapping" product **2** was obtained for the first time, we decided to introduce the trapping agent **3a** from the beginning of the reaction. Looking at the composition of the reaction mixture, introducing crotonate **3a** from the beginning it is somehow counterintuitive. In fact, not only ethyl crotonate **3a** is more reactive than benzoxazole **1b**, but also Cu/diphosphine ligand complexes and RMgBr are the reagents of choice for the conjugate addition to enoates.[5,9] When the crude reaction mixture was analysed, to our delight compound **4a** was the major product with only a small amount of product **5** and remarkably no significant traces of products derived from CA to compound **3a** (Scheme 6).



Scheme 6: One-pot ACA/enolate trapping of **1b** with ethyl crotonate **3a**.

Moreover **4a** was obtained in good yield (68%) and excellent enantiopurity (97%), due to the highly enantioselective conjugate addition of EtMgBr to **1b.** This change in reactivity order, with compound **1b** reacting faster than the theoretically more reactive compound **3a**, was unexpected. We tried to find the reasons behind this phenomenon having a closer look at the interactions that take place in the reaction mixture between the different components using NMR spectroscopy analysis (Figure 1).

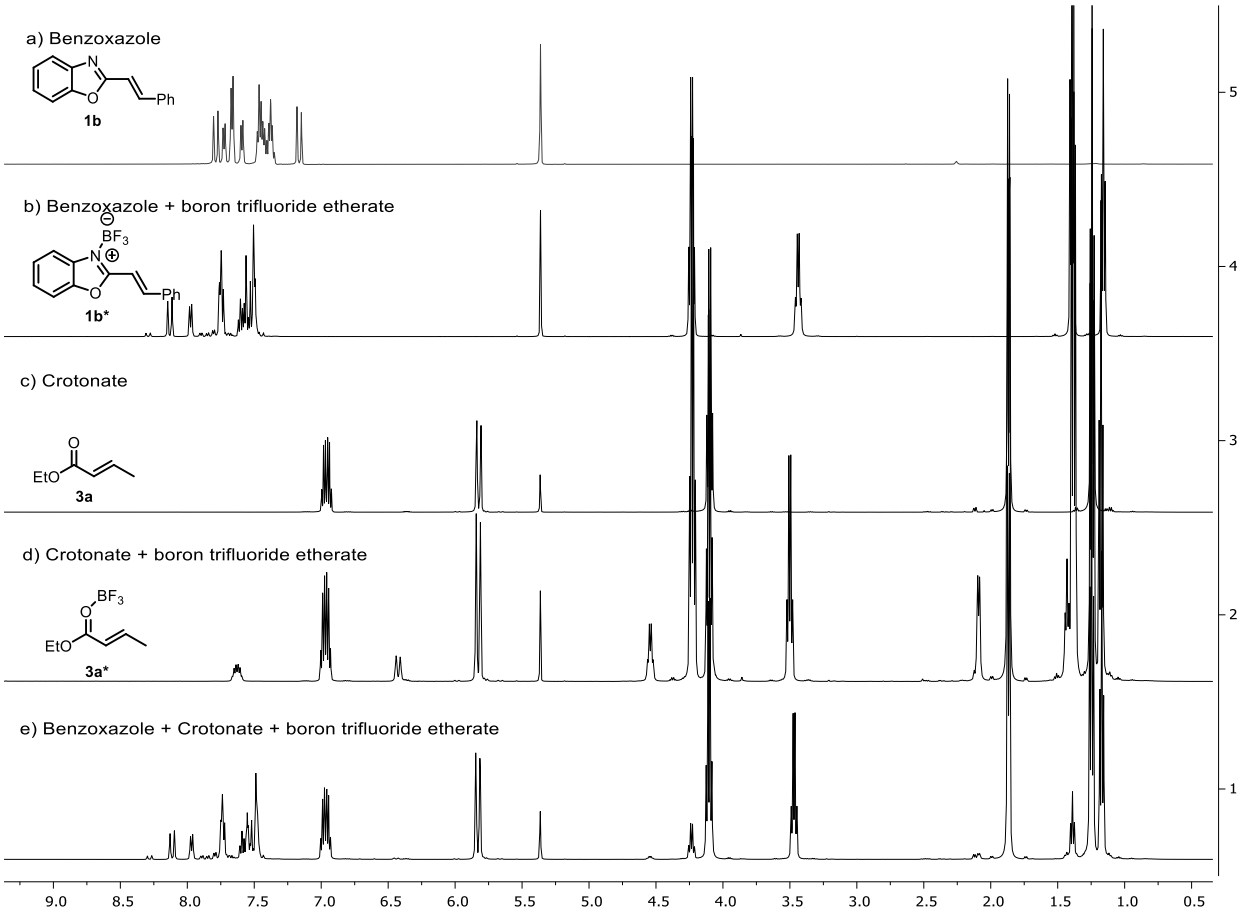
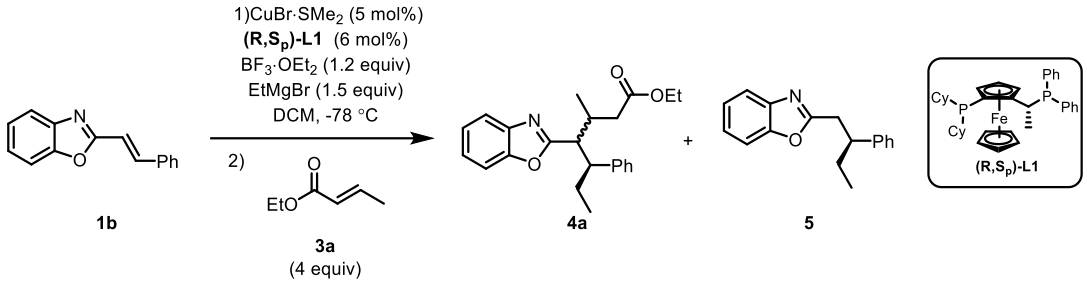


Figure 1: ^{1}H-NMR analysis of benzoxazole **1b**, crotonate **3a** and their corresponding complexes with $BF_3{\cdot}OEt_2$; Reaction condition: a) **1b** 0.1mmol, CD_2Cl_2 1ml, -60 °C; b) **1b** 0.1mmol, $BF_3{\cdot}OEt_2$ 1.2 equiv, CD_2Cl_2 1ml, -60 °C; c) **3a** 0.2mmol, CD_2Cl_2 0.5ml, -60 °C; d) **3a** 0.2mmol, $BF_3{\cdot}OEt_2$ 1.2 equiv,CD_2Cl_2 0.5ml, -60 °C; e) **1b** 0.12 mmol, **3a** 0.12 mmol, $BF_3{\cdot}OEt_2$ 1.0 equiv,CD_2Cl_2 1ml, -60 °C.

When to a solution of benzoxazole **1b** in CD_2Cl_2 (Figure 1a) is added $BF_3{\cdot}OEt_2$ (1.2 equiv) at -60 °C, complex **1b*** is readily formed as showed by the shift toward lower field of the peaks belonging to **1b** (Figure 1b). In contrast, ethyl crotonate **3a** (Figure 1c) is able to form only partially the complex **3a*** with $BF_3{\cdot}OEt_2$ (≈ 20%) (Figure 1d). When $BF_3{\cdot}OEt_2$ (1.0 equiv) is added to a solution of benzoxazole **1b** (1.2 mmol), ethyl crotonate **3a** (1.2 mmol) in CD_2Cl_2 (Figure 1e) only complex **1b*** is detected. It is clear that $BF_3{\cdot}OEt_2$ binds selectively to compound **1b** making it a better electrophile than ester **3a**, thus directing the addition of the Grignard reagent towards the newly formed complex **1b***. The reason behind higher conversion towards the enolate trapping in this reaction conditions is not fully understood. We hypothesized that in the reaction media an equilibrium between two enolate species, a boron enolate[10] and a magnesium enolate,[11] is established. One of the two is a highly reactive enolate with a relative short life time (kinetic enolate), that is replaced in time by the more stable and less reactive one (thermodynamic enolate). In this scenario, the immediate availability of the ester **3a** makes the trapping of the most reactive enolate possible. To support this hypothesis, a series of experiment were carried out varying the time gap between the addition of the Grignard reagent and **3a** (Table 1).

Table 1: Influence of the addition of crotonate **3a** at different time.



Entry	Time gap (h)	4a:5[a]	dr
1	0.0003 (1s)	80:20	6:1
2	3	50:50	6:1
3	16	40:60	2:1

[a] Determined via ^{1}H NMR spectroscopy analysis

As it is shown in Table 1, longer the time gap between the addition of the Grignard reagent and **3a** in the reaction media, lower the efficiency of the trapping process, which is supporting our initial hypothesis. Next, we tried to catch a glimpse of the nucleophilic intermediate and of its exchange, via NMR spectroscopy but the reaction mixture was too complex in order to detect any of these species. Considering that the substrate **1b** forms preferably a complex with $BF_3{\cdot}OEt_2$ that cannot be displaced by EtMgBr (Figure 2d), it is possible that at first the B-enolate is formed and it is more reactive.

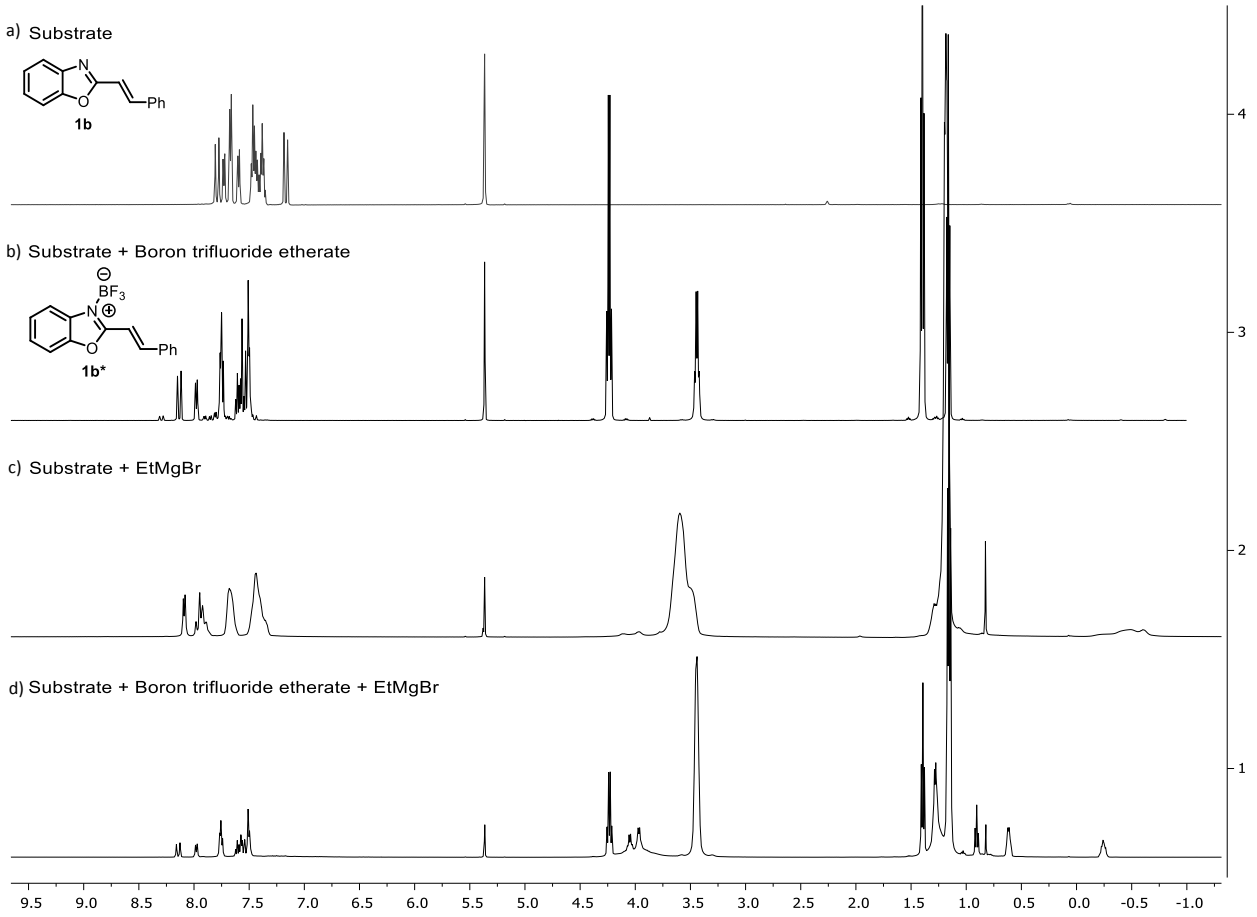
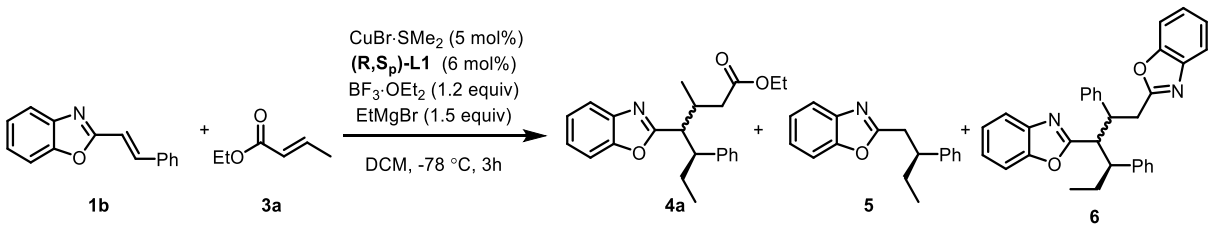


Figure 2: ^{1}H-NMR analysis of benzoxazole **1b** and its corresponding complexes with $BF_3{\cdot}OEt_2$ and EtMgBr; Reaction condition: a) **1b** 0.1mmol, CD_2Cl_2 1ml, -60 °C; b) **1b** 0.1mmol, $BF_3{\cdot}OEt_2$ 1.2 equiv, CD_2Cl_2 1ml, -60 °C; c) EtMgBr 0.075 mmol, CD_2Cl_2 0.5ml, -60 °C; d) **1b** 0.1mmol, EtMgBr 1.5 equiv, CD_2Cl_2 1ml, -60 °C.

In order to reach good conversion in carbonyl enolate trapping process, an excess of trapping agent, usually ranging from 1.5 to 2 equivalents, is required.[2] With the purpose to determine the optimal amount of trapping agent needed in our process, a series of experiments with different concentrations of ester **3a** were carried out (Table 2).

Table 2: Optimization of concentration of **3a**.



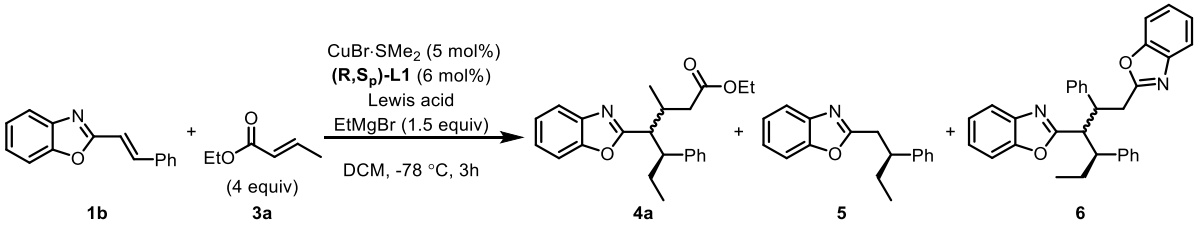
Equivalents of 3a	4a (%)[a]	5 (%)[a]	6 (%)[a]	dr 4a[a]
1.2	10	54	36	6:1
2	18	60	22	6:1
2.5	73	15	12	6:1
4	80	20	traces	6:1

[a] Determined via ^{1}H-NMR spectroscopy analysis

From this data it is clear that a large excess of ester **3a** is required in order to achieve high efficiency of the trapping process. When the amount of **3a** goes below 4 equivalents the auto-

trapping reaction becomes more prominent. This result is quite unexpected, since no auot-trapping product was observed in the ethylation of substrate **1b** in absence of **3a**.[6] This suggest that the presence of **3a** in the reaction media is somehow slowing the conjugate addition to compound **1b**, that is instead consumed as trapping agent favouring the formation of product **6**. To conclude our optimization studies, the effect of different Lewis acids was evaluated. The LAs have been chosen taking into account the previous study on the Cu catalysed conjugated addition to alkenyl aromatic heterocycles discussed in Chapter 2 (Table 3).[6]

Table 3: Lewis acid screening.



Entry	Lewis acid (equiv)	4a (%)[a]	5 (%)[a]	6 (%)[a]	dr [a]	*ee* (%)[b]
1	$BF_3{\cdot}OEt_2$ (1.2)	80	20	traces	6:1	97%
2	TMSOTf (1.2)	-	13	-	-	-
3[c]	TMSOTf (1.2)	-	50	-	-	Rac
4[c],[d]	TMSOTf (1.2)	-	50	-	-	Rac
5[c],[e]	TMSOTf (1.2)	-	68	-	-	Rac
6[c],[d],[e]	TMSOTf (1.2)	-	65	-	-	Rac
7	BCl_3 (1.2)	-	-	-	-	-
8	BBr_3 (1.2)	-	-	-	-	-

[a] Determined via ^{1}H- NMR spectroscopy analysis; [b] Determined via HPLC analysis; [c] Reaction carried out in absence of ester **3a**; [d] Reaction carried out in absence of chiral Cu-complex; [e]Reaction carried out with substrate **1a**.

When TMSOTf was tested in our enolate trapping protocol, only 13% conversion towards product **5** was detected (Table 3, entry 2). Interestingly when the TMSOTf was tested in the 1,4-addition to compound **1b**, only 50% of conversion was achieved with complete lack of enantioselectivity (*ee* = 0%)(Table 3, entry 3). Further experiments revealed that in presence of TMSOTf, the uncatalysed reaction took place exclusively (Table 3, entry 4). At first, the lower conversion was attributed to the steric hindrance of the Ph- group in the β-position, but this hypothesis was discarded when, subjecting compound **1a** to the same reaction conditions, similar results were obtained (Table 3, entries 5 and 6). Also in this case NMR analysis was chosen to understand why TMSOTf failed to promote the trapping process. As already mentioned, ethyl crotonate **3a** forms only partially a complex with $BF_3{\cdot}OEt_2$ (Figure 3b). On the other hand, when TMSOTf is considered, **3a** is fully converted in complex **3a‡** as indicated by the shift towards lower field of the vinylic proton observed in the NMR spectra (Figure 3c). The higher affinity of TMSOTf towards crotonate **3a**, in combination with its inferior capacity to promote the initial conjugate addition to **1b,** seems to be a possible explanation for the results obtained. To prove this hypothesis, TMSOTf was added to a solution of benzoxazole **1b** and crotonate **3a** (Figure 3e). Surprisingly and in sharp contrast with our findings, also in this case TMSOTf reacted exclusively with benzoxazole **1b**, showing the same selectivity as of $BF_3{\cdot}OEt_2$. Parasite reactions involving crotonate **3a** cannot be discarded and further investigation to identify them are needed.

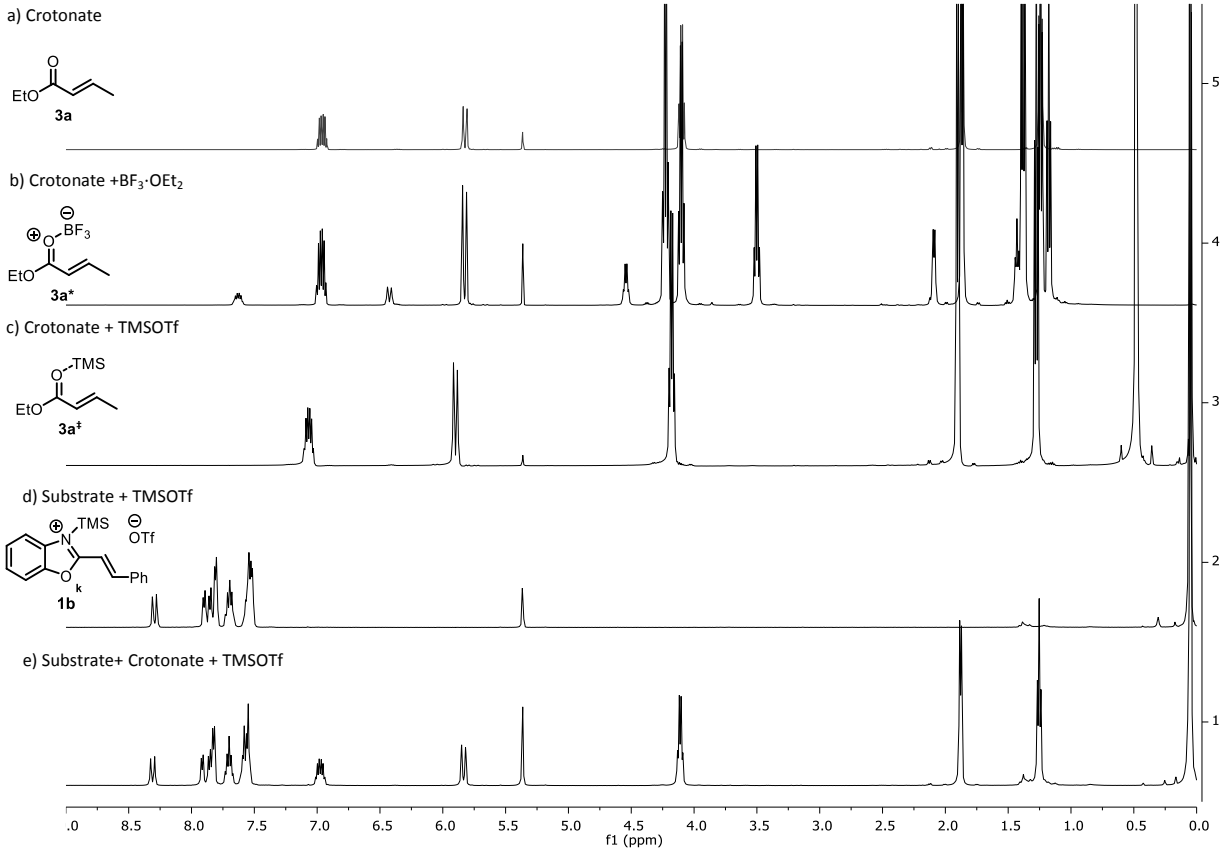


Figure 3: NMR analysis of substarte **1b** and crotonate **3a** and the corresponding complexes with $BF_3{\cdot}OEt_2$ and TMSOTf. Reaction condition: a) **3a** 0.2 mmol, CD_2Cl_2 0.5ml, -60 °C; b) **3a** 0.2mmol, $BF_3{\cdot}OEt_2$ 1.2 equiv,CD_2Cl_2 0.5ml, -60 °C; c) **3a** 0.2 mmol, TMSOTf 1.0 equiv, CD_2Cl_2 0.5ml, -60 °C; d) **1b** 0.05mmol, TMSOTf 1.2 equiv, CD_2Cl_2 0.5ml, -60 °C; e) **1b** 0.05mmol, **3a** 0.5 mmol, TMSOTf 1.2 equiv, CD_2Cl_2 0.5ml, -60 °C .

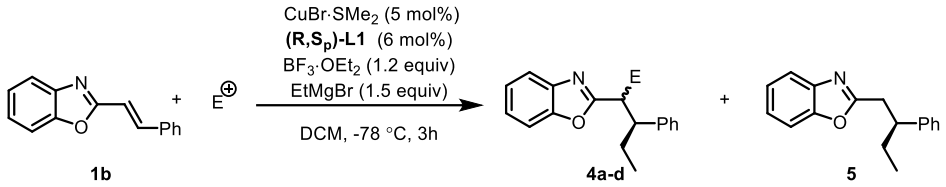
When BCl_3 and BBr_3 were used, no traces of compound **4a** or **5** were observed (Table 3, entries 7 and 8), while unknown side products ware formed predominantly. After isolation and full characterization, products were identified as compounds **7** and **8**, deriving from *N*-acylation of the 1,4-adduct enolate (Figure 4).

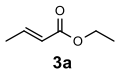
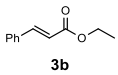
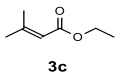
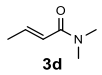
7 **8**

Figure 4: *N*-acylation products **7** and **8**.

A more careful look at the crude of the reaction promoted by $BF_3{\cdot}OEt_2$ revealed that compounds **7** and **8** are also formed in this reaction conditions, but in considerably lower amount (≈ 5%). This unexpected change of reactivity, strongly dependent on the nature of the boron Lewis acid, suggests that the actual nucleophilic species taking part in the catalytic cycle could be possibly a boron-enolate. From this short screening of Lewis acid, $BF_3{\cdot}OEt_2$ emerged as optimal LA for this transformation. With the optimized reaction conditions in our hands, the compatibility of different Michael acceptors with our protocol was tested (Table 4).

Table 4: Michael acceptors scope.



Entry	Electrophile	Product	4:5[a]	Yield (%)[b]	dr[a]	*ee* (%)[c]
1	 3a	**4a**	80:20	68	6:1	97
2	 3b	**4b**	76:24	49	2.5:1:1	91
3	 3c	**4c**	0:100	-	-	-
4	 3d	**4d**	27:73	N.D.	2.8:1	N.D.
5	 3e		0:100	-	-	-
6[d]	 3f		-	-	-	-
7 [d]	 3g		-	-	-	-
8 [d]	 3h		-	-	-	-
9 [d]	 3i		-	-	-	-

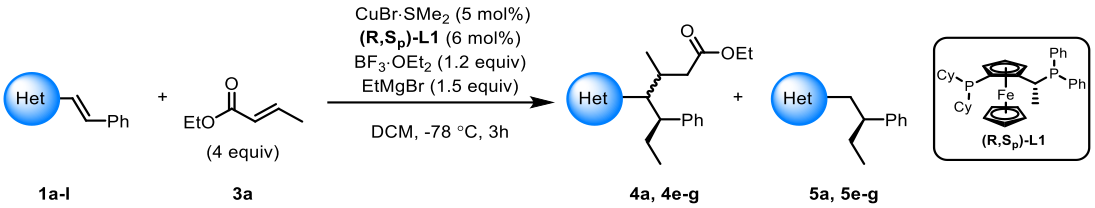
[a] Determined via ^{1}H-NMR spectroscopy analysis; [b] Isolated yields; [c] Determined via HPLC analysis; [d] Unreacted benzoxazole **1b** recovered.

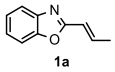
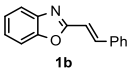
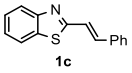
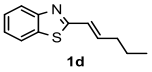
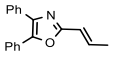
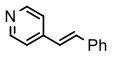
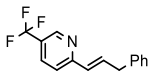
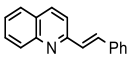
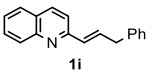
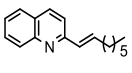
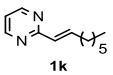
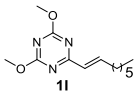
Unfortunately, beside ester **3a**, only ethyl cinnamate **3b** furnished the desired enolate trapping product in moderate yield and high enantioselectivity. Double substitution on the β-position of the trapping agent showed to be detrimental for the process. When β,β-substituted ester **3c** was employed only product **5** was obtained (entry 3, Table 2). *N,N*-dimethyl crotonamide **3d** showed some reactivity but to a lower extent compare with its ester analogue **1b,** as could be expected (entry 4, Table 2). In the presence of methyl acrylate **3f** and α,β-unsaturated lactone **3g**, conjugate and direct additions to the latter became the predominant process. The activation provided by $BF_3{\cdot}OEt_2$ failed to outcompete the abovementioned side reaction and starting material **1b** was recovered unreacted. α,β-Unsaturated carbonyl compound (entries 8, and 9, Table 1) showed similar results, with **1b** recovered unreacted at the end of the reaction. The lack of reactivity towards cinnamonitrile **3e** could be caused by its incompatibility with the low temperature at which the reaction is carried out (compound **3e** has a melting point of 18-20 °C). These results proved an extremely narrow scope of Michael acceptors for this one-pot procedure. Besides that, it also provide us a rough idea on the reactivity of compound **1b***, placing it in a hypothetical reactivity scale, between a ketone and an ester (Figure 5).

Figure 5: Hypothetical reactivity scale of Michael acceptors.

Our investigation continued by establishing the influence of the heterocyclic structure. Different aromatic heterocycles with different substitution at the β-position were subjected to our reaction conditions (Table 5).

Table 5: Heterocycle scope.



Entry	Substrates	Product	4:5[a]	Yield (%)[b]	dr[a]	*ee* (%)[c]
1	 1a	**4e**	77:23	53	3:1	79
2	 1b	**4a**	80:20	68	7:1	97
3	 1c	**4f**	60:40	58	3:1	93
4	 1d		0:100	-	-	-
5	 1e	**4g**	100:0	N.D.	4.4:3.6:1:1[d]	N.D.
6[e]	 1f	**4h**	36:64	N.D.	3:1	N.D.
7	 1g		-	-	-	-
8	 1h		-	-	-	-
9	 1i		-	-	-	-
10	 1j		0:100	-	-	-
11	 1k		0:100	-	-	-
12	 1l		0:100	-	-	-

[a] Determined via ^{1}H-NMR spectroscopy analysis; [b] Isolated yields; [c] Determined via HPLC analysis; [d] Determined via GC-MS; [e] 3 equiv of TMSOTf and 10% of chiral copper complex were used.

From the results of the screening of different heterocycles, it is clear that the structure of the aromatic heterocycle is crucial for the process to take place. Only benzoxazoles or structurally related substrates (Table 5, entries 1, 2, 3 and 5) delivered the desired enolate trapping product as main product. Among all the other substrates tested, only pyridine **1f** (Table 5, entry 6) showed a limited reactivity towards the trapping process. For pyridine **1g** (Table 5, entry 7) a complex reaction mixture with no clear signs of the corresponding trapping product was obtained. Quinoline **1h** (Table 5, entry 8) did not delivered any product and it was recovered unreacted, while quinoline **1i** (Table 5, entry 9) yielded a complex reaction mixture. Finally from compounds **1j**, **1k** and **1l** (Table 5, entries 10, 11, 12) only the corresponding 1,4 adducts were obtained. β-Substituent on the double bond exhibited a strong influence on the reactivity as well. While phenyl and methyl substituents were tolerated, longer aliphatic chains had a detrimental effect on the process (Table 5, entry 3 *vs* 4). Moreover phenyl group seemed to favour a better diastereoselectivity compare to methyl group (Table 5, entry 1 *vs* 2). Since compound **4f** was obtained as a crystal after slow evaporation from DCM, X-ray analysis was carried out to determine the absolute configuration of the two newly formed stereocentres (Figure 6).

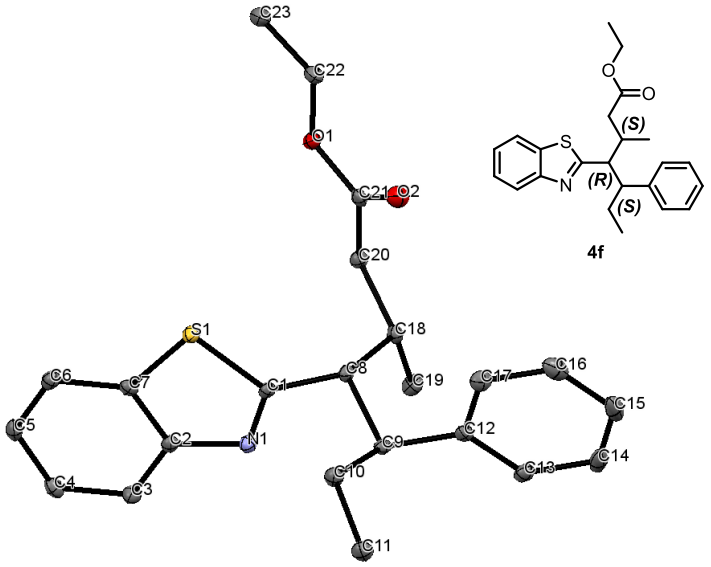


Figure 6: Molecular structure of compound **4f**, showing 50% probability ellipsoids. Hydrogen atoms are omitted for clarity.

The stereocentre at C8 position was found to be "*R*" while the other stereocentres at C18 and C9 were found to be "*S*" (Figure 6).

3.3 Conclusion

In conclusion, a one pot procedure for the trapping of heteroaromatic enolates with Michael acceptors was explored. The process exhibited high stereoselectivity, however high specificity for oxazole and benzoxazole derivatives. The same specificity was encountered during the electrophiles screening, limiting the scope of application to α,β-unsaturated esters. Interestingly, the superior affinity of $BF_3{\cdot}OEt_2$ towards the more Lewis basic benzoxazole resulted in a drastic change in reactivity order allowing the conjugate addition to the latter to occur in presence of more reactive esters. Moreover, it is possible to control the chemoselectivity of the reaction (*C*-alkylation *vs N*-acylation) by changing the structure of the boron LA. Extended studies on this

process and its dependence on the Lewis acid structure could furnish a new tool to achieve a better control on the selectivity of chemical processes.

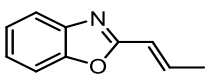
3.4 Experimental Section

3.4.1 General Information

All reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous solvents (*vide infr*a) under a nitrogen atmosphere using oven dried glassware and standard Schlenk techniques. Reactions were monitored by ^{1}H NMR. Purification of the products, when necessary, was performed by flash-column chromatography using Merck 60 Å 230-400 mesh silica gel. NMR data was collected on Bruker Avance NEO 600 (^{1}H at 600.0 MHz; ^{13}C at 150.87MHz), equipped with a Prodigy Cryo-probe, Varian Inova 500 (^{1}H at 500.0 MHz; ^{13}C at 125.72 MHz, ^{19}F at 470.37 MHz), equipped with an Indirect Detection probe and Varian VXR400 (^{1}H at 400.0 MHz; ^{13}C at 100.58 MHz, ^{19}F at 376.29, ^{31}P at 161.94 MHz), equipped with a 5 mm *z*-gradient broadband probe. Chemical shifts are reported in parts per million (ppm) relative to residual solvent peak ($CDCl_3$, ^{1}H: 7.26 ppm; ^{13}C: 77.16 ppm). Coupling constants are reported in Hertz. Multiplicity is reported with the usual abbreviations (s: singlet, bs: broad singlet, d: doublet, dd: doublet of doublets, ddd: doublet of doublet of doublets, t: triplet, td: triplet of doublets, q: quartet, dq: doublet of quartet, p: pentet, sex: sextet, hept: heptet, m: multiplet). Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI ionization. Enantiomeric excesses (*ee's*) were determined by Chiral HPLC analysis using a Shimadzu LC-10AD*VP* HPLC equipped with a Shimadzu SPD-M10A*VP* diode array detector and by Waters Acquity UPC2 system with PDA detector and QDA mass detector. Unless otherwise indicated, reagents and substrates were purchased from commercial sources and used as received. Solvents not required to be dry were purchased as technical grade and used as received. Dry solvents were freshly collected from a dry solvent purification system prior to use. Inert atmosphere experiments were performed with standard Schlenk techniques with dried (P_2O_5) nitrogen gas. Grignard reagents were purchased from Sigma-Aldrich and used as received (EtMgBr (3M in Et_2O). Unless otherwise noted substrates were prepared by literature reported methods (*vide infra*). Chiral ligand [**RevJosiphos**, (R,S_p)-**L1**] was purchased from Solvias. All reported compounds were characterized by ^{1}H and ^{13}C NMR and compared with literature data. All new compounds were fully characterized by ^{1}H and ^{13}C NMR and HRMS techniques.

3.4.2 Synthesis and Characterizations of Substrates

(*E*)-2-(prop-1-en-1-yl)benzoxazole (1a)

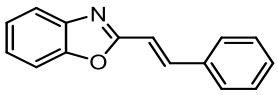


Compound **1** was prepared by literature procedure.[7] The product was obtained as a pale-yellow solid after silica gel chromatography (Pentane: EtOAC, 95:05, v/v). Yield = 78%. The NMR data are in agreement with the one present in literature.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 – 7.59 (m, 1H), 7.55 – 7.40 (m, 1H), 7.35 – 7.20 (m, 2H), 7.04 (dq, *J* = 15.9, 6.9 Hz, 1H), 6.46 (dq, *J* = 15.9, 1.8 Hz, 1H), 2.02 (dd, *J* = 6.9, 1.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.3, 150.1, 141.9, 139.0, 124.7, 124.2, 119.7, 118.2, 110.1, 18.7.

(*E*)-2-styrylbenzoxazole (1b)

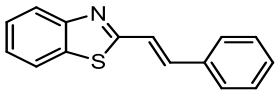


Compound **3a** was prepared by literature procedure.[7] The product was obtained as a white solid after crystallization in MeOH. Yield = 65%. The NMR data are in agreement with the one present in literature.[7]

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 16.3 Hz, 1H), 7.68-7.64 (m, 1H), 7.54 (m, 2H), 7.51-7.45 (m, 1H), 7.39-7.25 (m, 5H), 7.02 (d, *J* = 16.3 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 162.9, 150.5, 142.2, 139.6, 135.2, 129.9, 129.1, 127.7, 125.3, 124.6, 120.0, 114.0, 110.4.

(*E*)-2-styrylbenzothiazole (1c)

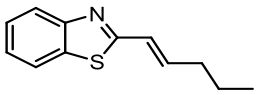


Compound **3b** was prepared by literature procedure.[7] The product was obtained as a white solid after crystallization in MeOH. Yield = 46%. The NMR data are in agreement with the one present in literature.[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.57 (m, 2H), 7.54 (d, *J* = 16.2 Hz, 1H), 7.48 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.45 – 7.34 (m, 5H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 137.7, 129.4, 128.9, 127.4, 126.3, 125.3, 122.9, 122.1, 121.5.

(*E*)-2-(pent-1-en-1-yl)benzothiazole (1d)

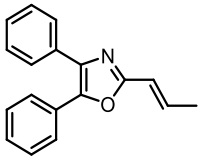


Compound **1j** was prepared by literature procedure.[7] The product was obtained as orange-yellow solid after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v). Yield = 71%. The NMR data are in agreement with the one present in literature.[7]

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 9.3 Hz, 1H), 7.39 (td, *J* = 8.3, 7.2, 1.3 Hz, 1H), 7.32 – 7.24 (m, 1H), 6.80 – 6.63 (m, 2H), 2.28 – 2.13 (m, 2H), 1.52 (sex, *J* = 7.4 Hz, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 167.3, 153.5, 141.7, 133.9, 125.9, 124.9, 124.6, 122.6, 121.2, 34.8, 21.6, 13.6.

(*E*)-4,5-diphenyl-2-(prop-1-en-1-yl)oxazole (1e)

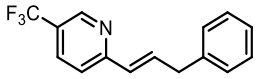


Compound **1l** was prepared by literature procedure.[7] The product was obtained as pale yellow solid after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v). Yield = 66%. The NMR data are in agreement with the one present in literature.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.67 (m, 2H), 7.67 – 7.56 (m, 2H), 7.49 – 7.21 (m, 6H), 6.85 (dq, *J* = 15.8, 6.9 Hz, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 1.96 (dd, *J* = 6.9, 1.8 Hz, 3H).

^{13}C NMR (101 MHz, $cdcl_3$) δ 159.8, 144.6, 136.1, 135.4, 132.6, 129.0, 128.6, 128.5, 128.4, 128.1, 128.0, 126.5, 117.8, 18.6.

(*E*)-2-(3-phenylprop-1-en-1-yl)-5-(trifluoromethyl)pyridine (1g)

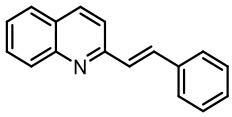


Compound **1g** was prepared by literature procedure.[7] The product was obtained as pale yellow liquid after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v). Yield = 50%

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.85 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.53 – 7.27 (m, 5H), 7.24 (q, *J* = 7.3, 5.9 Hz, 1H), 6.57 (d, *J* = 15.9 Hz, 1H), 6.43 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.82 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 164.4, 146.5 (q, *J* = 3.9 Hz), 137.1, 133.7 (q, *J* = 3.5 Hz), 132.9, 128.7, 127.6, 126.4, 126.2, 122.7, 42.0.

(E)-2-styrylquinoline (1h)

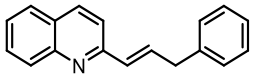


Compound **1h** was prepared by literature procedure.[7] The product was obtained as white solid after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v). Yield = 91%. The NMR data are in agreement with the one present in literature.[12]

^{1}H NMR (400 MHz, $CDCl_3$): δδ 8.13 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 9.3 Hz, 1H), 7.78 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.74 – 7.61 (m, 5H), 7.50 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.45 – 7.36 (m, 3H), 7.36 – 7.28 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.3, 148.6, 136.9, 136.7, 134.8, 130.1, 129.5, 129.3, 129.1, 129.0, 127.8, 127.7, 127.6, 126.5, 119.6.

(E)-2-(3-phenylprop-1-en-1-yl)quinoline (1i)



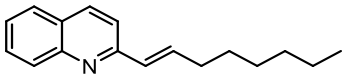
Compound **1p** was prepared by literature procedure.[7] The product was obtained as colorless oil after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v). Yield = 76%

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 8.1, 2.8 Hz, 2H), 7.74 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.68 (ddd, *J* = 8.5, 6.9, 1.5 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.47 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.38 – 7.21 (m, 4H), 6.96 (dt, *J* = 15.9, 6.8 Hz, 1H), 6.78 (dt, *J* = 15.8, 1.5 Hz, 1H), 3.67 (d, *J* = 6.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.0, 148.0, 139.2, 136.1, 136.0, 132.1, 129.5, 129.1, 128.8, 128.5, 127.4, 127.1, 126.3, 125.9, 118.7, 39.4.

HRMS (ESI$^+$): *m/z* calcd. for $C_{18}H_{16}N$ ([M+H$^+$])246.12790, measured mass: 246.12773

(*E*)-2-(oct-1-en-1-yl)quinolone (1j)

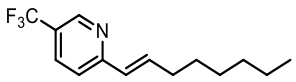


Compound **1p** was prepared by literature procedure.[7] The product was obtained as colorless oil after silica gel flash-chromatography (Pentane: EtOAC, 95:05, v/v). Yield = 91%. The NMR data are in agreement with the one present in literature.[1]

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 – 7.95 (m, 2H), 7.76 – 7.59 (m, 2H), 7.55 – 7.34 (m, 2H), 6.90 – 6.76 (m, 1H), 6.70 (d, *J* = 15.9 Hz, 1H), 2.30 (q, *J* = 7.2 Hz, 2H), 1.52 (quin, *J* = 7.3 Hz, 2H), 1.42 – 1.19 (m, 6H), 0.97 – 0.79 (m, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 156.5, 148.0, 138.0, 136.1, 131.0, 129.5, 129.1, 127.4, 127.1, 125.8, 118.7, 33.1, 31.7, 29.0, 28.9, 22.6, 14.1.

***(E)*-2-(oct-1-en-1-yl)-5-(trifluoromethyl)pyridine (3b)**



Compound **3b** was synthesized according to the literature procedure.[7] The product was isolated as colorless oil after flash-column chromatography (Pentane:EtOAc, 99:1, v/v), Yield = 56%. The NMR data are in agreement with the one present in literature.[7]

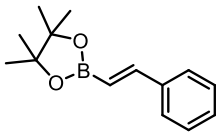
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.4 Hz, 1H), 7.81 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.32 (d, *J* = 8.3 Hz, 1H), 6.89 (dt, *J* = 15.6, 7.0 Hz, 1H), 6.52 (d, *J* = 15.6 Hz, 1H), 2.29 (q, *J* = 7.1 Hz, 2H), 1.51 (p, *J* = 7.2 Hz, 2H), 1.42 – 1.21 (m, 6H), 0.88 (t, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 146.4 (q, *J* = 4.2 Hz), 139.6, 133.9, 133.7, 133.5 (q, *J* = 3.5 Hz) , 128.9, 128.8, 128.6, 128.5, 124.1 (q, *J* = 32.9 Hz), 123.9 (q, *J* = 271.75 Hz), 120.4, 33.0, 31.8, 29.1, 28.9, 22.7, 14.1

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.3.

HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{18}F_3N$ ([M+H$^+$]) 258.14641, measured mass: 258.14651

(E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (9)



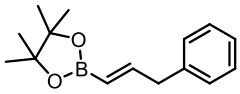
Compound **9** was synthesized according to the literature procedure.[7] The product was isolated as colorless oil after flash-column chromatography (Pentane:EtOAc, 99:1, v/v), Yield = 87%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.47 (m, 2H), 7.40 (d, *J* = 18.5 Hz, 1H), 7.36 – 7.28 (m, 3H), 6.17 (d, *J* = 18.5 Hz, 1H), 1.32 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.1, 140.1, 131.5, 131.2, 129.7, 86.0, 27.5.

HRMS (ESI$^+$): *m/z* calcd. for $C_{14}H_{20}BO_2$ ([M+H$^+$]) 231.15509, measured mass: 231.15324.

(E)-4,4,5,5-tetramethyl-2-(3-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane (10)



Compound **10** was synthesized according to the literature procedure.[7] The product was isolated as colorless oil after flash-column chromatography (Pentane:EtOAc, 99:1, v/v), Yield = 53%

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.26 (m, 2H), 7.23 – 7.15 (m, 3H), 6.78 (dt, *J* = 17.8, 6.3 Hz, 1H), 5.47 (dt, *J* = 17.8, 1.6 Hz, 1H), 3.49 (dd, *J* = 6.3, 1.6 Hz, 2H), 1.26 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 138.9, 128.8, 128.3, 126.0, 82.9, 42.1, 24.7.

HRMS (ESI$^+$): *m/z* calcd. for $C_{15}H_{22}BO_2$ ([M+H$^+$]) 245.17074, measured mass: 245.17078.

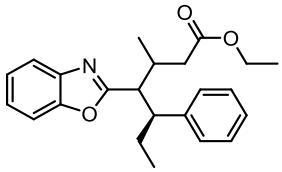
3.4.3 General Procedure A: Enantioselective Conjugate Addition/Trapping Process

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, CuBr·SMe_2 (5 mol%), and ligand (*R*,*S*$_p$)-**L1** (6 mol%) were dissolved in CH_2Cl_2 (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and BF_3·OEt_2 (1.2 equiv) was added. After 5 min the trapping agent (4.0 equiv) was added followed by EtMgBr (1.5 equiv). After stirring at -78 °C for 3h, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH_4Cl and warmed to RT. The reaction extracted with CH_2Cl_2 (3 × 10 mL). Combined organic phases were dried over $MgSO_4$, filtered and solvents were evaporated on rotary evaporator. The oily crude was purified by chromatography on silica gel using mixture of pentane and EtOAc as eluent.

3.4.4 General Procedure B: Racemic Conjugate Addition/Trapping Process

In a heat dried Schlenk tube equipped with septum and magnetic stirring bar, $CuBr{\cdot}SMe_2$ (5 mol%), and ligand (±)-**BINAP** (6 mol%) were dissolved in CH_2Cl_2 (1mL/0.1mmol of substrate) and stirred under nitrogen atmosphere for 15 min. The substrate (1.0 equiv) was added at once. After stirring for 5 min. at RT the reaction mixture was cooled to -78 °C and $BF_3{\cdot}OEt_2$ (1.2 equiv) was added. After 5 min the trapping agent (4.0 equiv) was added followed by EtMgBr (1.5 equiv). After stirring at -78 °C for 3h, the reaction was quenched with MeOH (1 mL) followed by saturated aqueous solution of NH_4Cl and warmed to RT. The reaction extracted with CH_2Cl_2 (3 × 10 mL). Combined organic phases were dried over $MgSO_4$, filtered and solvents were evaporated on rotary evaporator. The oily crude was purified by chromatography on silica gel using mixture of pentane and EtOAc as eluent.

Ethyl 4-(benzoxazol-2-yl)-3-methyl-5-phenylheptanoate (4a)



Compound **4a** was synthesized following general procedure A with 0.mmol of **1b**,$BF_3{\cdot}OEt_2$ (0.12 mmol, 1.2 equiv), EtMgBr (3M in Et_2O, 0.15 mmol, 1.5 equiv), $CuBr{\cdot}SMe_2$ (0.005 mmol, 5 mol%), ligand (R,S_p)-**L1** (0.006 mmol, 6 mol%), **3a** (0.4 mmol, 4 equiv), in 1mL CH_2Cl_2. Product **4a** was obtained as pale-yellow oil after flash-column chromatography (SiO_2, Pentane:EtOAc 97:3, v/v), [68% yield, 97% ee].

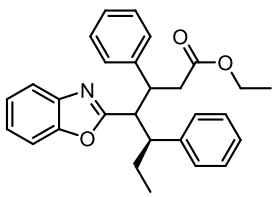
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.75 (dd, *J* = 6.3, 3.0 Hz, 1H), 7.55 (dd, *J* = 6.4, 2.9 Hz, 1H), 7.41 – 7.32 (m, 4H), 7.30 – 7.23 (m, 3H), 4.09 (qt, *J* = 7.1, 3.7 Hz, 2H), 3.57 (dd, *J* = 11.6, 3.6 Hz, 1H), 3.19 (td, *J* = 11.0, 3.6 Hz, 1H), 2.26 – 2.05 (m, 2H), 1.93 (dd, *J* = 15.1, 6.5 Hz, 1H), 1.51 – 1.32 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.60 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 172.4, 167.3, 150.6, 141.8, 141.3, 128.7, 128.4, 126.9, 124.7, 124.4, 120.0, 110.7, 60.4, 49.2, 48.5, 40.3, 30.8, 28.9, 14.6, 14.3, 12.0.

HRMS (ESI$^+$): *m/z* calcd. for $C_{23}H_{28}NO_3$ ([M+H$^+$]) 366.20689, measured mass: 366.20637.

CSP-HPLC: (206 nm, Chiralcel OD-H, *n*-heptane:*i*PrOH = 95:5, 40 °C, 0.5 ml/min.), t_R = 7.99 min (major), t_R = 13.02 min (minor).

Ethyl 4-(benzoxazol-2-yl)-3,5-diphenylheptanoate (4b)



Compound **4b** was synthesized following general procedure A with 0.mmol of **1b**,$BF_3{\cdot}OEt_2$ (0.12 mmol, 1.2 equiv), EtMgBr (3M in Et_2O, 0.15 mmol, 1.5 equiv), $CuBr{\cdot}SMe_2$ (0.005 mmol, 5 mol%), ligand (R,S_p)-**L1** (0.006 mmol, 6 mol%), **3b** (0.4 mmol, 4 equiv), in 1mL CH_2Cl_2. Product **4a** was

obtained as pale-yellow oil after flash-column chromatography (SiO_2, Pentane:EtOAc 97:3, v/v), [49% yield, 91% ee].

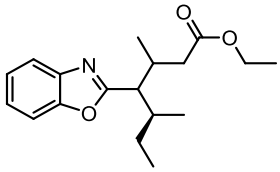
^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.73 (dd, *J* = 7.0, 2.4 Hz, 1H), 7.45 – 7.37 (m, 3H), 7.37 – 7.28 (m, 3H), 7.29 – 7.22 (m, 2H), 7.17 – 7.04 (m, 3H), 6.65 (d, *J* = 6.8 Hz, 2H), 4.00 (dddd, *J* = 17.9, 10.8, 7.1, 3.7 Hz, 2H), 3.92 (dd, *J* = 11.2, 4.4 Hz, 1H), 3.49 (td, *J* = 7.8, 4.4 Hz, 1H), 2.99 (td, *J* = 10.5, 4.0 Hz, 1H), 2.94 – 2.83 (m, 1H), 2.57 (dd, *J* = 16.0, 7.7 Hz, 1H), 1.48 – 1.36 (m, 2H), 1.09 (t, *J* = 7.1 Hz, 3H), 0.56 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): 171.7, 166.3, 150.4, 141.8, 141.0, 139.4, 128.9, 128.8, 128.6, 127.7, 127.0, 126.8, 124.7, 124.2, 119.9, 110.5, 60.3, 49.7, 48.0, 42.4, 39.0, 28.4, 14.0, 11.5.

HRMS (ESI$^+$): *m/z* calcd. for $C_{28}H_{30}NO_3$ ([M+H$^+$])428.2220, measured mass: 428.2224

CSP-HPLC: (233 nm, Chiralcel OD-H, *n*-heptane:*i*PrOH = 95:5, 40 °C, 0.5 ml/min.), t_R = 8.51 min (major), t_R = 9.23 min (minor).

Ethyl 4-(benzoxazol-2-yl)-3,5-dimethylheptanoate (4d)



Compound **4d** was synthesized following general procedure A with 0.mmol of **1a**,$BF_3{\cdot}OEt_2$ (0.12 mmol, 1.2 equiv), EtMgBr (3M in Et_2O, 0.15 mmol, 1.5 equiv), $CuBr{\cdot}SMe_2$ (0.005 mmol, 5 mol%), ligand (*R,S$_p$*)-**L1** (0.006 mmol, 6 mol%), **3b** (0.4 mmol, 4 equiv), in 1mL CH_2Cl_2. Product **4d** (inseparable mixture of diastereoisomers) was obtained as pale-yellow oil after flash-column chromatography (SiO_2, Pentane:EtOAc 97:3, v/v), [53% yield, 79% ee].

^{1}H-NMR (400 MHz, $CDCl_3$, Major): δ 7.72 – 7.67 (m, 1H), 7.52 – 7.46 (m, 1H), 7.34 – 7.27 (m, 2H), 4.18 – 4.08 (m, 2H), 2.90 (dd, *J* = 9.7, 5.4 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.37 (dd, *J* = 15.6, 5.6 Hz, 1H), 2.13 – 1.93 (m, 2H), 1.24 (t, *J* = 7.2 Hz, 3H), 1.22 – 1.14 (m, 2H), 1.03 (dd, *J* = 9.4, 6.7 Hz, 6H), 0.83 (t, *J* = 7.4 Hz, 3H).

^{1}H-NMR (400 MHz, $CDCl_3$, Minor): δ 7.73 – 7.66 (m, 1H), 7.53 – 7.45 (m, 1H), 7.34 – 7.27 (m, 2H), 4.19 – 4.07 (m, 2H), 2.97 (t, *J* = 7.6 Hz, 1H), 2.73 – 2.61 (m, 1H), 2.44 (dd, *J* = 15.4, 5.2 Hz, 1H), 2.14 – 1.91 (m, 2H), 1.59 – 1.47 (m, 1H), 1.37 – 1.24 (m, 1H), 1.25 (t, *J* = 7.2 Hz, 2H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H).

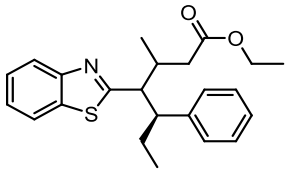
^{13}C NMR (101 MHz, $CDCl_3$, Major): δ 172.6, 167.6, 150.4, 141.1, 124.4, 124.1, 119.8, 110.4, 60.4, 50.1, 40.4, 34.8, 30.4, 27.2, 16.6, 15.2, 14.2, 11.1.

^{13}C NMR (101 MHz, $CDCl_3$, Minor): δ 172.5, 167.6, 150.4, 141.1, 124.4, 124.1, 119.7, 110.4, 60.4, 49.2, 39.9, 34.6, 30.3, 27.0, 16.4, 16.2, 14.3, 10.9.

HRMS (ESI$^+$): *m/z* calcd. for$C_{18}H_{26}NO_3$ ([M+H$^+$])304.1907, measured mass: 304.1911

CSP-HPLC: (233 nm, Chiralcel OD-H, *n*-heptane:*i*PrOH = 99.8:0.2, 40 °C, 0.5 ml/min.), t_R = 21.15 min (major), t_R = 27.13 min (minor).

Ethyl 4-(benzothiazol-2-yl)-3-methyl-5-phenylheptanoate (4f)



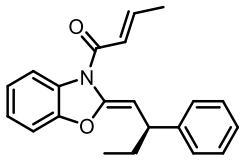
Compound **4f** was synthesized following general procedure A with 0.1 mmol of **1c**,$BF_3{\cdot}OEt_2$ (0.12 mmol, 1.2 equiv), EtMgBr (3M in Et_2O, 0.15 mmol, 1.5 equiv), $CuBr{\cdot}SMe_2$ (0.005 mmol, 5 mol%), ligand (R,S_p)-**L1** (0.006 mmol, 6 mol%), **3b** (0.4 mmol, 4 equiv), in 1mL CH_2Cl_2. Product **4f** was obtained as pale-yellow solid after flash-column chromatography (SiO_2, Pentane:EtOAc 97:3, v/v), [58% yield, 95% ee]. After purification product **4f** was dissolved in CH_2Cl_2 and recrystallized by slow evaporation.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 8.06 (d, *J* = 8.1 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.49 (t, *J* = 7.3 Hz, 1H), 7.44 – 7.33 (m, 3H), 7.29 (d, *J* = 6.9 Hz, 3H), 4.20 – 4.00 (m, 2H), 3.71 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.12 (td, *J* = 10.8, 3.7 Hz, 1H), 2.27 – 2.11 (m, 2H), 1.97 – 1.87 (m, 1H), 1.56 – 1.39 (m, 2H), 1.31 – 1.17 (m, 3H), 1.01 (d, *J* = 6.6 Hz, 3H), 0.58 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 175.1, 174.2, 155.8, 144.8, 137.4, 131.2, 131.0, 129.3, 128.5, 125.5, 124.0, 62.8, 55.8, 53.1, 42.8, 33.6, 31.2, 17.1, 16.9, 14.6.

HRMS (ESI$^+$): *m/z* calcd. for $C_{23}H_{28}O_2S$ ([M+H$^+$])328.1835, measured mass: 382.1839

(E)-1-((Z)-2-((S)-2-phenylbutylidene)benzoxazol-3(2H)-yl)but-2-en-1-one (7)

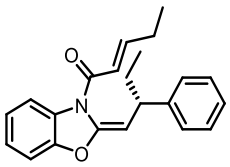


^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.81 – 7.68 (m, 1H), 7.55 (ddd, *J* = 8.6, 6.2, 3.8 Hz, 1H), 7.35 (ddt, *J* = 7.3, 4.4, 1.6 Hz, 1H), 7.32 – 7.23 (m, 3H), 7.23 – 7.17 (m, 2H), 7.12 (dq, *J* = 8.4, 7.0 Hz, 1H), 6.82 (dq, *J* = 15.6, 6.9 Hz, 1H), 6.06 (dq, *J* = 15.6, 1.6 Hz, 1H), 4.70 (d, *J* = 11.1 Hz, 1H), 3.69 (qd, *J* = 10.8, 3.6 Hz, 1H), 1.73 (ddd, *J* = 6.9, 1.7, 0.8 Hz, 3H), 1.68 – 1.56 (m, 2H), 0.67 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.1, 162.8, 151.2, 145.3, 141.2, 140.7, 130.4, 128.6, 128.5, 127.0, 125.3, 124.63, 120.2, 111.0, 57.1, 48.0, 27.1, 18.5, 11.7.

HRMS (ESI$^+$): *m/z* calcd. for $C_{21}H_{22}NO_2$ ([M+H$^+$])320.16510, measured mass: 320.16451

(E)-1-((E)-2-((*S*)-2-phenylbutylidene)benzoxazol-3(2H)-yl)pent-2-en-1-one (8)



^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.55 (ddd, *J* = 8.6, 6.2, 3.8 Hz, 1H), 7.41 – 7.32 (m, 2H), 7.32 – 7.23 (m, 2H), 7.23 – 7.16 (m, 2H), 7.16 – 7.08 (m, 1H), 7.06 – 6.99 (m, 1H), 6.41 (dd, *J* = 15.6, 1.7 Hz, 1H), 4.63 (d, *J* = 11.1 Hz, 1H), 3.69 (qd, *J* = 10.8, 3.7 Hz, 1H), 1.91 (ddd, *J* = 6.9, 1.7, 0.8 Hz, 3H), 1.57 – 1.43 (m, 2H), 0.75 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 193.7, 162.3, 150.9, 146.1, 141.2, 141.0, 130.5, 128.4, 128.3, 126.8, 124.9, 124.2, 119.9, 110.6, 57.3, 48.0, 27.5, 18.7, 12.0.

HRMS (ESI$^+$): *m/z* calcd. for $C_{21}H_{22}NO_2$ ([M+H$^+$])320.16510, measured mass: 320.16451

3.4.5 Crystallographic Data

A single crystal of compound **4f** was mounted on top of a cryoloop and transferred into the cold nitrogen stream (100 K) of a Bruker-AXS D8 Venture diffractometer. Data collection and reduction was done using the Bruker software suite APEX3.[13] The final unit cell was obtained from the xyz centroids of 9898 reflections after integration. A multiscan absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (*SADABS*). The structures were solved by direct methods using *SHELXT*[14] and refinement of the structure was performed using *SHLELXL*.[15] The hydrogen atoms were generated by geometrical considerations, constrained to idealised geometries and allowed to ride on their carrier atoms with an isotropic displacement parameter related to the equivalent displacement parameter of their carrier atoms. The absolute configuration of the model was chosen based on anomalous dispersion. Refinement of the Flack x parameter converged on 0.031(5). Crystal data and details on data collection and refinement are presented in Table S1

Table S1: Crystallographic data for **4f**

chem formula	C23 H27 N O2 S
M_r	381.51
cryst syst	orthorhombic
color, habit	colorless, platelet
size (mm)	0.15 x 0.13 x 0.03
space group	P 21 21 21
a (Å)	7.2805(2)
b (Å)	9.1009(2)
c (Å)	30.6730(7)
V (Å^3)	2032.37(9)
Z	4
ρ_{calc}, g.cm^{-3}	1.247
μ(Cu K$\overline{\alpha}$), cm^{-1}	1.542
F(000)	816
temp (K)	100(2)
θ range (deg)	5.069 – 70.014
data collected (h,k,l)	-8:8, -11:10, -37:35
no. of rflns collected	18635
no. of indpndt reflns	3802
observed reflns	3649 ($F_o \geq 2\,\sigma(F_o)$)
R(F) (%)	2.60
wR(F^2) (%)	6.41
GooF	1.108
Weighting a,b	0.0298, 0.3780
params refined	247
Restraints	0
min, max resid dens	-0.262, 0.221
Flack x	0.031(5)

3.5 Biblography

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